UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/597,753	09/20/2006	Rene Hersperger	33647-US-PCT	5799

75074 7590 02/03/2010

NOVARTIS INSTITUTES FOR BIOMEDICAL RESEARCH, INC.
220 MASSACHUSETTS AVENUE
CAMBRIDGE, MA 02139

EXAMINER	
MABRY, JOHN	

ART UNIT	PAPER NUMBER
1625	

MAIL DATE	DELIVERY MODE
02/03/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/597,753	HERSPERGER ET AL.	
	Examiner	Art Unit	
	JOHN MABRY	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 November 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6-8,11-13 and 15* is/are pending in the application.

4a) Of the above claim(s) *6,11-13 and 15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 7 and 8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Response to Applicant's Remarks

Applicant's response on November 18, 2009 filed in response to the Office Action dated October 20, 2009 has been received and duly noted.

In view of this response, the status of the rejections/objections of record is as follows:

Status of the Claims

Claims 1-3, 7 and 8 are pending and rejected.

Claims 4, 5, 9, 10 and 14 have been cancelled.

Claims 6, 11-13 and 15 directed towards non-elected subject matter.

Claim 15 is new.

35 USC § 112 Rejection(s)

The 112-2nd rejection of claims 1-3, 7 and 8 regarding the term "linker" have been overcome in view of Applicants amendment to the claim

The 112-1st rejection of claims 1-3, 7 and 8 regarding the term "prodrug" have not been overcome in view of Applicant's amendment. Applicant has amended said claims to read "ester" and have deleted the term "prodrug". However, an ester is considered a prodrug, especially in view of Applicant's definition as shown in Specification on page 4. As previously stated in last office action, Applicants provide no guidance as how the compounds are made more active *in vivo*. The choice of "esters (prodrugs)" will vary

from drug to drug. Therefore, more than minimal routine experimentation would be required to determine which prodrugs will be suitable for the instant invention.

The instant compounds of formula (I) wherein the esters (prodrugs) are not described in the disclosure in such a way the one of ordinary skill in the art would no how to prepare the various compounds suggested by said claims. In view of the lack of direction provided in the specification regarding starting materials, the lack of working examples, and the general unpredictability of chemical reactions, it would take an undue amount of experimentation for one skilled in the art to make the claimed compounds and therefore practice the invention.

The 112-1st rejection of claims 1-3, 7 and 8 regarding the scope of enablement for "R" have not been overcome in view of Applicant's arguments. Examiner has clearly stated that Applicant is enabled for the following: R being unsubstituted alkyl, benzofuran optionally substituted with Cl, but does not reasonably provide enablement for R being the full scope as claimed along with all claimed substituents, for instant terms like "substituted", "heteroaryl", "aryl" and "heterocyclic" and heteroaryloxy". Examiner maintains the Applicant is not enabled for the claimed scope of variable R and claimed substituents.

Applicant argues that pages 22-23 and experimental section of Specification discloses numerous conditions known in the chemical art which can enable an ordinary skill artisan how to make compounds of Formula I where R is all that is claimed. Applicant stated that R can be introduced by displacement of a bromo substituent of

intermediate VI by using Suzuki coupling reactions. Applicant also states that Suzuki coupling is well known to be applicable to a large range of heteroaryl boronic acids and that a large number of acids are commercially readily available.

In response to Applicant's arguments, Examiner has provided the following remarks only in view of Applicant's arguments and to support Examiner's initial rejections.

According to US 6,838,585, organoboron reagents are disadvantageous because of limited availability, incompatibility with non-polar organic solvents and difficulties in purification (see column 2, lines 50-55).

For instance, according the definition of the terms "heteroaryl" and "substituents" as defined in the Specification s as follows:

> The optional substituent or substituents on R and R9 are independently selected from the group consisting of halogen, hydroxy, C_1-C_7 alkyl, mono or di-lower alkylamino, aminocarbonyl, mono or di-lower alkylaminocarbonyl, amino, carboxy, C_1-C_7 alkoxy, C_3-C_{12} cycloalkyl, C_3-C_{18} heterocycloalkyl, C_1-C_7 alkylcarbonyl, C_1-C_7 alkoxycarbonyl, nitryl, aryl; all of which, except halogen, are independently optionally substituted by one or more substituents, selected from the group consisting of halogen, hydroxyl, C_1-C_7 alkyl, mono or di- C_1-C_7 alkylamino, aminocarbonyl, mono or di- C_1-C_7 alkylaminocarbonyl, amino, carboxy, C_1-C_7 alkoxy, C_3-C_{12} cycloalkyl, C_3-C_{18} heterocycloalkyl, C_1-C_7 alkylcarbonyl, C_1-C_7 alkoxycarbonyl, nitryl, aryl.

Actually, the term “heteroaryl” is not explicitly defined in the Specification. Examiner will used the most closely related term, heterocyclic, which encompasses the term "heteraryl" as shown below and on page 4 of the Specification.

> Heterocyclic aryl is an aromatic monocyclic or bicyclic hydrocarbon containing from 5 to 18 ring atoms one or more of which are heteroatoms selected from O, N or S. Preferably there are one or two heteroatoms. Heterocyclic aryl represents, for example: pyridyl, indolyl, quinoxalinyl, quinolinyl, isoquinolinyl, benzothienyl, benzofuranyl, benzopyranyl, benzothiopyranyl, furanyl, pyrrolyl, thiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl, pyrazolyl, imidazolyl, thienyl. Heterocyclic aryl also includes such substituted radicals.

Again, Applicant stated that a large range of heteroaryl boronic acids are commercially readily available. According to the Sigma-Aldrich Catalog, the world's leading supplier of biochemical and organic chemical products, and found only the following heteroaryl boronic acid reagents: thiophenyl, pyrazolyl, furanyl, 1,3-pyrimidinyl, pyridinyl, benzothiophenyl, benzofuranyl, indolyl, quinolinyl and isoquinolinyl (see Sigma-Aldrich Catalog attached).

As previously stated, it is not trivial to experimentally interchange any and all of the many substituents that exist. As described by F. Zaragoza Dörwald, most organic syntheses fail initially and chemical research is highly inefficient due to chemists spending most of their time "finding out what went wrong and why". Therefore, most syntheses of organic compounds are labor-intensive and demanding. Additionally, most final synthetic routes to desired organic molecules are usually very different from initially planned routes. A highly skilled chemist can agree that for many successful organic compounds made, many failures are encountered and experimental repetition is common. This also contributes to the burden and unpredictability of the syntheses of said compounds. (see “Side Reactions in Organic Synthesis: A Guide to Successful Synthesis Design" 2005 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

Based on the disadvantages of boronic acid derivatives, use of these derivatives in Suzuki coupling and lack of starting material, it would clearly cause an undue burden on an ordinary skilled artisan in the chemical art to perform and reproduce the claimed invention.

Claim Rejections - 35 USC § 102

Claims 1, 2, 4, 5, 7 and 8 rejections are withdrawn under 35 U.S.C. 102(e) as being anticipated by US 7,078,419 in view of Applicant’s remarks. After further consideration, an obviousness rejection over US ‘419 is made below.

Claim Rejections - 35 USC § 103

Claims 1, 2, 4, 5, 7 and 8 rejections are withdrawn under 35 U.S.C. 103(a) as being unpatentable over US 6,465,485 (PTO-1449) in view of Applicant's amendments to the claims.

An action on the merits of claims 1-3 and 7-8 is contained herein below.

DETAILED ACTION

Claim Objection

Claim 7 is objected to as being dependent upon cancelled claim 5.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

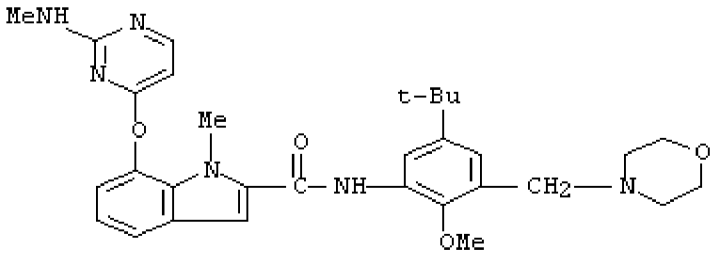
Claims 1, 2, 3, 7 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 7,078,419.

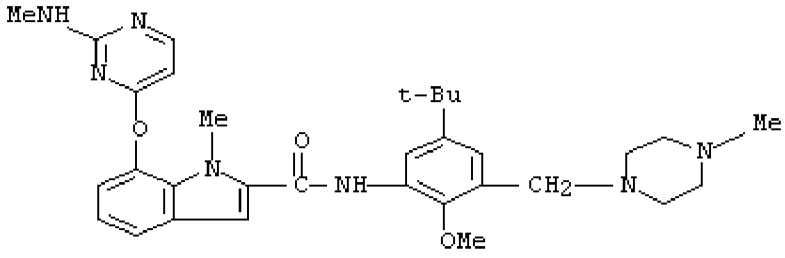
Note: Regarding claim 7, regardless of how the compounds are made, which could be through a different process than described in claim 6, it is still obvious. When the reference teaches a product that appears to be the same, or an obvious variant of, the product set forth in a product-by-process claim although produced by a different process. See *In re Marosi,* 710 F.2d 799, 218USPQ 289 (Fed. Cir. 1983) and *In re Thorpe,* 777 F.2d 695, 227 USPQ 964 (Fed. Cir. 1985).

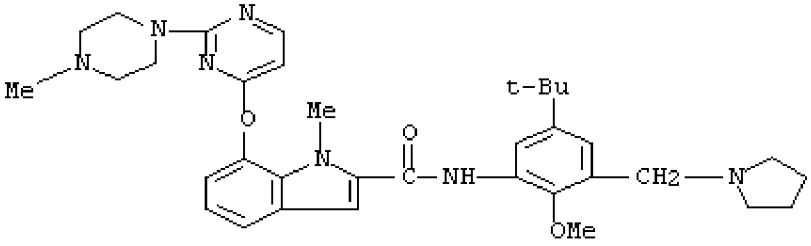
The instant application claims compounds and pharmaceutical compositions of Formula I where Z=NR3 where R3 is methyl; R9=H; R=O-heteroaryl; X=phenyl; Q=CH2CH2 and Y=piperidinyl, azepanyl, azocanyl, tetrahydropyranyl and 8-aza-bicyclo[3.2.1]oct-8-yl.

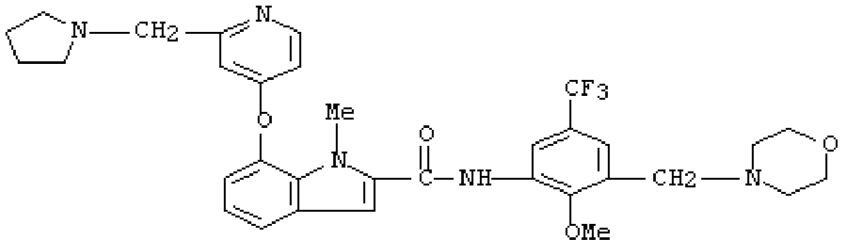
Scope & Content of Prior Art MPEP 2141.01

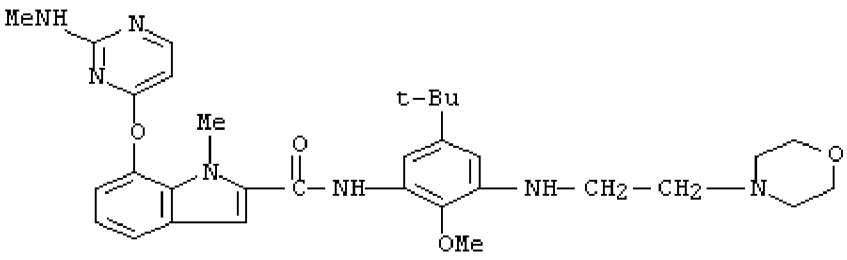
US '419 discloses compounds and pharmaceutical compositions of Formula I wherein Z=NR3 where R3 is methyl; R9=H; R=O-pyridinyl, O-1,3-pyrimidinyl; X=phenyl; Q=CH2, NHCH2CH2 and Y=morpholinyl, piperazinyl, pyrrolinyl (as shown below and bottom of columns 29/30; top of columns 31/32; middle of columns 33/34; and middle of columns 89/90).











Differences between Prior Art & the Claims MPEP 2141.02

US '419 differs from instantly claimed invention at: (a) the position of R on phenyl portion of the indole ring: US '419's –O-heteroaryl at the 6-position versus Applicant's –O-heteroaryl at the 4-position which are positional isomers and (b) the Y position – US 419's morpholinyl, piperazinyl, pyrrolinyl versus Applicant's piperidinyl, azepanyl, azocanyl, tetrahydropyranyl and 8-aza-bicyclo[3.2.1]oct-8-yl.

It is well established that position isomers are prima facie structurally obvious even in the absence of a teaching to modify. The isomer is expected to be prepared by the same method and to have generally the same properties. This expectation is then deemed the motivation for preparing the position isomers. This circumstance has arisen many times. See: *Ex parte Englehardt,* 208 USPQ 343, 349; *In re Mehta,* 146 USPQ 284, 287; *In re Surrey*, 138 USPQ 67; *Ex Parte Ullyot,* 103 USPQ 185; *In re Norris,* 84 USPQ 459; *Ex. Parte Naito,* 168 USPQ 437, 439; *Ex parte Allais,* 152 USPQ 66; *In re Wilder,* 166 USPQ 545, 548; *Ex parte Henkel,* 130 USPQ 474; *Ex parte Biel,* 124 USPQ 109; *In re Petrzilka,* 165 USPQ 327; *In re Crownse,* 150 USPQ 554; *In re Fouche,* 169 USPQ 431; *Ex parte Ruddy,* 121 USPQ 427; *In re Wiechert,* 152 USPQ 249, *In re Shetty,* 195 USPQ 753; *In re Jones,* 74 USPQ 152, 154. There may be others as well. Thus, said claims are rendered obvious by US '485 et al.

For example, "Position isomerism has been used as a tool to obtain new and useful drugs" (*Englehardt*) and "Position isomerism is fact of close structural similarity" (*Mehta*, emphasis in the original). Note also *In re Jones,* 21 USPQ2d 1942, which

states at 1943 "Particular types or categories of structural similarity without more, have, in past cases, given rise to prima facie obviousness"; one of those listed is "adjacent homologues and structural isomers". Position isomers are the basic form of close "structural isomers." Similar is *In re Schechter and LaForge,* 98 USPQ 144, 150, which states "a novel useful chemical compound which is homologous or isomeric with compounds of the prior art is unpatentable unless it possesses some unobvious or unexpected beneficial property not possessed by the prior art compounds." Note also *In re Deuel* 34 USPQ2d 1210, 1214 which states, "Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds…a known compound may suggest it analog or isomers, either geometric (cis v. trans) or position isomers (e.g. *ortho v. para*)." See also MPEP 2144.09, second paragraph. Further, the reference provides for the ring being substituted in any position.

US '419 teaches that Ar1 (which corresponds to claimed variable Y) can be substituted with R1 where R1 equals heterocycle (see column 8, lines 1-25). US '419 defines the term heterocycle as the following (see column 96):

The term "heterocycle" refers to a stable nonaromatic 4–8 membered (but preferably, 5 or 6 membered) monocyclic or nonaromatic 8–11 membered bicyclic heterocycle radical which may be either saturated or unsaturated. Each heterocycle consists of carbon atoms and one or more, preferably from 1 to 4 heteroatoms chosen from nitrogen, oxygen and sulfur. The heterocycle may be attached by any atom of the cycle, which results in the creation of a stable structure. Unless otherwise stated, heterocycles include but are not limited to, for example pyrrolidinyl, pyrrolinyl, morpholinyl, thiomorpholinyl, thiomorpholinyl sulfoxide, thiomorpholinyl sulfone, dioxalanyl, piperidinyl, piperazinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrofuranyl, 1,3-dioxolanone, 1,3-dioxanone, 1,4-dioxanyl, piperidinonyl, tetrahydropyrimidonyl, pentamethylene sulfide, pentamethylene sulfoxide, pentamethylene sulfone, tetramethylene sulfide, tetramethylene sulfoxide and tetramethylene sulfone.

Prima Facie Obviousness, Rational & Motivation MPEP 2142-2413

It would be obvious for an artisan of ordinary skill in the art to place the heteroaryloxy group at any position about the phenyl ring of the indole ring in view of the teachings and case law was cited above and to replace a finite number of heterocyclyl group at the Y position in view of teachings mentioned above.

The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in KSR noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit. The Court quoting In re Kahn, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006), stated that "[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with

some rational underpinning to support the legal conclusion of obviousness.'" KSR, 550 U.S. at___, 82 USPQ2d at 1396. Exemplary rationales that may support a conclusion of obviousness include:

(A) Combining prior art elements according to known methods to yield predictable results;

(B) Simple substitution of one known element for another to obtain predictable results;

(C) Use of known technique to improve similar devices (methods, or products) in the same way;

(D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results;

(E) "Obvious to try" – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;

(F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art;

(G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention. See MPEP § 2143 for a discussion of the rationales listed above along with examples illustrating how the cited rationales may be used to support a finding of obviousness. See also MPEP §

2144- §2144.09 for additional guidance regarding support for obviousness determinations.

The aforementioned reasons above describe rationales that support a conclusion of obviousness based upon the KSR International Co. *v.* Teleflex Inc. decision. Letters (A) - (E) rationale is supported above.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to John Mabry, PhD whose telephone number is (571) 270-1967. The examiner can normally be reached on M-F from 9am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's primary examiner can be reached at (571) 272-0684, first, or the Examiner's supervisor, Janet Andres, PhD, can be reached at (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/John Mabry/
Examiner
Art Unit 1625

/Rita J. Desai/
Primary Examiner, Art Unit 1625